REMARKS

Claims 1, 3, 5, 7, 9, 11 and 21-35 are amended herein. Claim 20 is canceled, and new Claims 37-48 are added herein. Support for the amendments to Claims 1, 3, 5, 7, 9, 11 and 23-34, can be found throughout the specification, for example, on page 4, lines 24-31. Support for the amendments to Claims 21 and 22 is found throughout the specification and the claims as originally filed, for example at original Claims 17-19. The amendment to Claim 35 is merely grammatical and does not alter the scope of Claim 35. Support for new claims 37-48 is found throughout the specification, for example, at page 17, lines 8-16 and 24-30, page 18, lines 1-9, and Figures 1-3. The amendments to the claims and new claims do not add new matter.

Claims 1-12 and 21-48 are presented for examination.

Objection to the Specification

The Office Action has objected to the amendment to the specification. The Office Action states that the deletion of lines 21-23 on page 3 constitutes new matter. The deletion of lines 21-23 on page 3 was made to remove subject matter already present at lines 18-20 on page 3. Thus, this deletion in no way added to or removed subject matter from the specification. Accordingly, Applicants submit that the amendment to the specification did not add new matter.

Rejection of the claims under 35 U.S.C. §112, Second Paragraph

Claims 20-22 are rejected as indefinite because one skilled in the art allegedly would not be able to determine the metes and bounds of "sequence motif." Claim 20 is canceled herein, and Claims 21 and 22 are amended to depend from Claim 1. Accordingly, this ground for rejection of the claims is moot.

Claims 35 and 36 are rejected as indefinite because Claim 35 allegedly fails to conform with current U.S. practice.

Applicants respectfully traverse this rejection.

Applicants submit that Claim 35 as previously submitted was fully compliant with well-established practice under 37 CFR §1.75(e). However, for the purposes of expediting

prosecution, Applicants have amended Claim 35 for further clarity and with no intent to alter the scope of the claim in any way. Applicants maintain that Claim 35 as amended is fully compliant with practice under 37 CFR §1.75(e). Accordingly, Applicants respectfully request that the Examiner remove this ground for rejection of the claims.

Rejection Under 35 U.S.C §112, First Paragraph

Claims 1-12 and 20-34 stand rejected under 35 U.S.C § 112, first paragraph, as containing subject matter, which was allegedly not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants respectfully traverse.

To satisfy the written description requirement, a patent application must describe the invention in sufficient detail that one of skill in the relevant art could conclude that the inventor was in possession of the claimed invention at the time the application was filed. *See Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563-64, (Fed. Cir. 1991). According to the Federal Circuit, it is clear that Applicants need not precisely recite each and every element of a claim limitation in the specification in order to satisfy the written description requirement. *See Union Oil of Cal. v. Atlantic Richfield Co.*, 208 F.3d 989 (Fed. Cir. 2000). Information that is well known in the art need not be described in detail in the specification, and is preferably omitted. *See, e.g., Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 USPQ 81, 90 (Fed. Cir. 1986). In particular, it is unnecessary under the written description requirement for the specification to provide structures of nucleic acid molecules whose structures are known in the art, particularly when the functions of those nucleic acid molecules are known. *Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005)* ("The chimeric genes here at issue are prepared from known DNA sequences of known function. The Board's requirement that these sequences must be analyzed and reported in the specification does not add descriptive substance.").

The Office Action states that the specification does not disclose a specific structure that corresponds with the function of being antisense, as claimed.

Applicants address this rejection first as it applies to Claims 1, 3 and 5 and claims dependent therefrom, and second as it applies to Claims 7, 9 and 11, and claims dependent therefrom.

Claims 1, 3 and 5, and claims dependent therefrom

Claims 1, 3 and 5 are directed to improved antisense oligonucleotides, where the improvement includes one or more base of the antisense oligonucleotide being a non-naturally occurring base selected from the group consisting of a degenerate base, 5-nitroindole, 3-nitropyrrole, 4-nitrobenzimidazole, and nebularine. As such, Claims 1, 3 and 5 acknowledge that antisense oligonucleotides are known in the art, and indicate that the claimed improvements include the recited modification(s) to said antisense oligonucleotides. Thus, the claims recite antisense oligonucleotide structures, which are known in the art, as modified by the recited improvements. It is unnecessary under the written description requirement for the specification to provide structures of nucleic acid molecules whose structures are known in the art. *Capon v. Eshhar, 418 F.3d 1349 (Fed. Cir. 2005).* One skilled in the art need not be taught known nucleic acid structures with known functions.

The Office Action states that the specification does not disclose a specific structure that corresponds with the function of being antisense. There is no requirement that a specification teach the structural basis for the function of a compound with a known structure and a known function (See *Capon, supra*). The claims recite antisense oligonucleotide structures, which are known in the art, as modified by the recited improvements. There is no requirement that the specification teach such known antisense oligonucleotide structures. Accordingly, Applicants respectfully request removal of the rejection under 35 U.S.C § 112, first paragraph, of Claims 1, 3 and 5, and claims dependent therefrom.

Claims 7, 9 and 11, and claims dependent therefrom

Claims 7, 9, and 11, and claims dependent therefrom, are also fully described in the specification. Guidance to specific RNase recruiting regions and targeting regions are provided

in the specification and one of skill in the art readily appreciates the structural elements that are recited in the claims.

For example, Claim 7, as amended, is directed to an antisense oligonucleotide comprising an RNA targeting region and a RNase L-recruiting region comprising a 2'-5' adenosine oligomer, wherein the RNA targeting region of said antisense oligonucleotide comprises one or more non-naturally occurring base selected from the group consisting of degenerate base, 5-nitroindole, 3-nitropyrrole, 4-nitrobenzimidazole, and nebularine. The specification provides specific guidance on the structure of a RNase L-recruiting region. For example, the specification at page 3, lines 1-5, page 7, lines 10-13, and page 10, line 10, through page 11, line 3, teaches specific structural details for region that recruits RNase L. The specification also cites U.S. Patent No. 5,583,032 for structure of regions that recruit RNase L. Furthermore, Claim 7 recites that the RNase L-recruiting region comprises a 2'-5' adenosine oligomer. Accordingly, the specification teaches, and Claim 7 recites, specific structure that corresponds with the function of being a RNase L-recruiting region.

The Office Action presents no evidence that one skilled in the art would not understand the structural requirements for RNase L recruitment. In fact, the Office Action has acknowledged the teachings in the art relating to the antisense activity of RNase L recruiting domains. For example, the Office Actions states:

> Torrance et al. teach the advantages of RNase L recruiting regions in antisense applications wherein they disclose chimeric antisense oligonucleotides that comprise 4, 2'-5' linked adenosines (an RNase L-recruiting region) and an a [sic] 3',5'-deoxyribonucleotide antisense sequence (an RNA targeting region) (column 24, example 7), show that 2-5A greatly enhances the ability of an antisense oligonucleotide to inhibit specific gene expression (column 33, lines 28-35) and teach that, 'Because 2-5A-dependent RNase is believed to be present in most mammalian cells, the therapeutic control of protein translation for the treatment of cancer, viral infections, genetic diseases, osteoarthritis, rheumatoid arthritis, restinosis, and a variety of other medical conditions can be accomplished using this technology' (column 34, lines 62-67). Office Action at 16-17.

Thus, it is acknowledged that an RNase L recruiting region greatly enhances the ability of an antisense oligonucleotide to inhibit specific gene expression. As such, it is established that the structure of an RNase L recruiting region is correlated with the function of being antisense.

Therefore, one skilled in the art would understand the structure of the antisense oligonucleotide of Claim 7. Accordingly, the antisense oligonucleotide of Claim 7, in view of the knowledge in the art, is fully described by the specification.

Claim 9, as amended, is directed to an antisense oligonucleotide comprising an RNA targeting region and a RNase P-recruiting region, wherein the RNA targeting region of said antisense oligonucleotide comprises one or more non-naturally occurring base selected from the group consisting of degenerate base, 5-nitroindole, 3-nitropyrrole, 4-nitrobenzimidazole, and nebularine. The specification provides specific guidance on the structure of a RNase P-recruiting region. For example, the specification at page 7, lines 14-18, page 10, line 10, through page 11, line 3, and SEQ ID NO:11, teaches specific structural details for regions that recruit RNase P. The specification also cites U.S. Patent No. 5,877,162 and the publication by Ma et al. (Antisense Nucl. Acid Drug Dev. 8:415-426, 1998) for structure of regions that recruit RNase P. Accordingly, those skilled in the art readily appreciate the specific structures that correspond with the function of being a RNase P-recruiting region.

The Office Action presents no evidence that one skilled in the art would not understand the structural requirements for RNase P recruitment. In fact, the Office Action has acknowledged the teachings in the art relating to the antisense activity of RNase P recruiting domains. For example, the Office Actions states:

> Krupp teaches that [sic] advantages of RNase P in antisense applications wherein he recites, '[t]he RNase P approach can combine attractive features from both established systems: similar to ribozyme systems the free choice between extracellular addition of oligoribonucleotides or intracellular production of RNA transcripts; like the RNase H approach, it takes advantage of. the efficiency of a normal cellular enzyme' (pg. 136, column 2, 3rd paragraph) and 'RNase P combines the advantages of a ubiquitous cellular enzyme (like RNase H) with the possible choice between short, synthetic antisense oligoribonucleotides and large, in vivo RNA transcripts (like hammerhead ribozymes)' (pg. 138, conclusions, 1st paragraph).
>
> ***
>
> [M]odifications to antisense oligonucleotides comprising the addition of an RNase L or P recruiting region were known in the art to provide the benefits of increased duplex stability as well as to operate by recruiting a naturally occurring enzyme

> such as an RNase L or P to greatly enhance the efficiency of the multivalent oligonucleotide to inhibit gene expression via the degradation of multiple target mRNA transcripts. Office Action at 17-18.

Thus, it is acknowledged that an RNase P recruiting region greatly enhances the ability of an antisense oligonucleotide to inhibit specific gene expression. As such, it is established that the structure of an RNase P recruiting region is correlated with the function of being antisense. Therefore, one skilled in the art would understand the structure of the antisense oligonucleotide of Claim 9. Accordingly, the antisense oligonucleotide of Claim 9, in view of the knowledge in the art, is fully described by the specification.

Claim 11, as amended, is directed to a ribozyme comprising an RNA targeting region, which comprises one or more non-naturally occurring base selected from the group consisting of degenerate base, 5-nitroindole, 3-nitropyrrole, 4-nitrobenzimidazole, and nebularine. The specification provides specific guidance on the structure of a ribozyme. For example, the specification at page 9, line 31, through page 10, line 6, teaches a specific type of ribozyme, and references the publication by Benseler et al. (J. Am. Chem. Soc. 115:8483-8484, 1993) for additional ribozyme structural details. Accordingly, the specification teaches and points to a reference that teaches specific structural details that correspond with the function of being a ribozyme.

The Office Action presents no evidence that one skilled in the art would not understand the structural requirements for ribozyme activity. Thus, the specification teaches and points to a reference that teaches specific structural details that correspond with the function of being a ribozyme, and there is no evidence that one skilled in the art would not understand the structure of the ribozyme of Claim 11. Accordingly, the ribozyme of Claim 11, in view of the knowledge in the art, is fully described by the specification.

In view of the above, Applicants submit that Claims 7-12 and 20-34, fully comply with the written description requirement because the claimed subject matter was described in the specification in such a way as to convey to one skilled in the art that the inventors had possession

of the claimed invention. Accordingly, Applicants respectfully request that the rejection of Claims 7-12 under 35 U.S.C § 112, first paragraph, be removed.

Rejection Under 35 U.S.C. § 102

Claims 1-6, 20-25 and 29-32 are rejected under 35 U.S.C. § 102(a) as being anticipated by Nyce et al., WO 99/13886, published March 25, 1999.

Applicants respectfully traverse this rejection.

Nyce is not prior art under 35 U.S.C. § 102(a). Applicants submit that they conceived of the invention and diligently reduced it to practice prior to the publication by Nyce. As evidence of this prior conception, Applicants submit herewith Exhibit 1, a Declaration by Bob D. Brown, an inventor of the presently claimed subject matter of this application. As attested to in the Declaration, the claimed invention was conceived of and diligently reduced to practice prior to the publication by Nyce on March 25, 1999, as demonstrated by the exhibit provided in the Brown Declaration. In view of the foregoing, Nyce is not prior art to the present application under 35 U.S.C. § 102(a). Accordingly, Applicants respectfully request that the Examiner remove this ground for rejection of the claims.

Rejections Under 35 U.S.C. §§ 102 and 103

Claims 1-6, 20-25 and 29-32 are rejected under 35 U.S.C. §§ 102(b) or 103(a) as being anticipated by or obvious over Bergstrom et al. (U.S. Pat. No. 5,681,947).

Applicants respectfully traverse this rejection.

The Office Action indicates that Bergstrom discloses "antisense oligonucleotide therapeutics directed toward nucleic acid targets which have significant variability." Office Action at 11 (emphasis added).

Claims 1, 3, and 5, and claims dependent therefrom, as presently amended, are directed toward antisense oligonucleotides that are able to hybridize to two or more RNA molecules that differ in sequence by one or more single nucleotide polymorphism (SNP) in the target regions that hybridize to said antisense oligonucleotide.

Bergstrom teaches antisense therapeutics toward nucleic acid targets having "significant variability." In contrast, the claims are directed to antisense oligonucleotides that target RNAs which differ in sequence by one or more single nucleotide polymorphism (SNP). SNPs are regions of single polymorphisms and are not regions of "significant variability." Bergstrom does not teach or suggest antisense oligonucleotides directed to SNPs. Moreover, Bergstrom does not teach or suggest the desirability of antisense oligonucleotides directed to SNPs because Bergstrom teaches targeting regions of significant variability. If anything, Bergstrom's teaching of targeting regions of significant variability would lead one skilled in the art away from the presently claimed antisense oligonucleotides that target RNAs, which differ in sequence by one or more SNPs. As such, the claimed antisense oligonucleotides are neither anticipated by, nor obvious over, Bergstrom.

Claims 1-6 and 20-25 are rejected under 35 U.S.C. §§ 102(b) or 103(a) as being anticipated by or obvious over Guo et al. WO 97/46711.

Applicants respectfully traverse this rejection.

The Office Action states that Guo teaches oligonucleotides containing universal bases and RNase H recruiting domains.

Guo teaches oligonucleotidses with RNase H recruiting domains. Guo does not teach or suggest any composition that target RNAs, which differ in sequence by one or more SNPs. Moreover, Guo teaches nothing whatsoever regarding antisense targeting of oligonucleotides. Accordingly, nothing in Guo would lead one of ordinary skill in the art to arrive at the claimed antisense oligonucleotides. As such, the claimed antisense oligonucleotides are neither anticipated by, nor obvious over, Guo.

Rejection Under 35 U.S.C. § 103

Claims 1-12 and 20-34 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Bergstrom et al. in view of Werther et al. (US Patent 5,929,040) , Torrence et al. (U.S. Pat. No. 5,583,032), and Krupp (Biochemie 75:135-139 1993).

Applicants respectfully traverse this rejection.

To establish a *prima facie* case of obviousness a three-prong test must be met. First, there must be some suggestion or motivation, either in the references or in the knowledge generally available among those of ordinary skill in the art, to modify the reference. Second, there must be a reasonable expectation of success found in the prior art. Third, the prior art must teach or suggest all the claim elements. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

Applicants respectfully submit that the cited art does not render Claims 1-12 and 20-34 *prima facie* obvious because the cited art, alone or in any combination, fails to teach or suggest all claim elements.

Claims 1, 3, 5, 7, 9 and 11, and claims dependent therefrom, are directed to antisense oligonucleotides and ribozymes that target RNAs which differ in sequence by one or more single nucleotide polymorphism (SNP).

Bergstrom provides one sentence on the use of antisense oligonucleotides directed to nucleic acid targets that have "significant variability." Single nucleotide polymorphisms (SNPs) and are not regions of "significant variability." Bergstrom does not teach, suggest, or motivate the design of antisense oligonucleotides directed to SNPs because Bergstrom only describes targeting regions of significant variability. If anything, Bergstrom's one sentence on the design of antisense oligonucleotides targeted to regions of significant variability would lead one skilled in the art away from the presently claimed antisense oligonucleotides that target RNAs, which differ in sequence by one or more SNPs.

Werther, Torrance and Krupp, alone or in combination, do not teach or suggest that which is lacking in Bergstrom. None of these references teaches or suggests antisense oligonucleotides directed to SNPs or the desirability of targeting nucleic acid molecules with SNPs. Accordingly, none of Bergstrom, Werther, Torrance or Krupp, alone or combined, teach, suggest or motivate the design of the claimed subject matter. As such, the claimed antisense oligonucleotides are not obvious over the cited references, and Applicants respectfully request that this rejection be withdrawn.

CONCLUSION

In view of the above, Applicants submit that claims are now in condition for allowance and such action is earnestly solicited. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11 1410.

Respectfully submitted,

KNOBBE, MARTENS, OLSON & BEAR, LLP

Dated: 3-March-06

By: _____

Kerry Taylor
Registration No. 43,947
Attorney of Record
Customer No. 20,995
(619) 235-8550

2410880
030306